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CHANGES IN THE INCIDENCE AND CHARACTER OF TUBERCULOSIS PRODUCED BY PRECEDING INFECTION

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Present knowledge concerning the portal of entry of the tubercle bacillus, the dissemination of infection from the air passages or the digestive tract to internal organs, the relation of bovine tuberculosis to human infection, and the influence of immunity upon the prophylaxis and treatment of the disease have been so ably expounded that there is little excuse for again presenting a general survey of any one of these subjects. One aspect of the disease has, I believe, excited comparatively little general interest. It was formerly our habit to believe that the tuberculous lesion was dependent upon the localization, the number and the virulence of the tubercle bacillus which had entered the body. There is abundant evidence that susceptibility to tuberculosis is modified by previous infection, but furthermore, the relative susceptibility of different tissues, for example, of the lungs and of lymphatic nodes; the rapidity with which cells accumulate at the site of invasion by tuberle bacilli, the occurrence of caseation, the tendency to cavity formation in the lungs, and the new formation of fibrous tissue are profoundly modified by pre-existing infection.

The view is now widely accepted that tuberculosis in most instances is transmitted from one human being to another by bacilli thrown off from a cavity within the infected lung; there is as yet no agreement concerning the mode of transmission whether by moist droplets discharged by coughing with expired air or by dust derived from dried sputum containing tubercle bacilli or by other means. Bacteria reach the upper air passages, the mouth and pharynx and there is still much conflicting discussion of the question, whether infection of the lung occurs primarily or is secondary to invasion through the mucous membranes of mouth, pharynx or intestine into the lymphatic nodes which are tributary to these parts. Although this transmission from lung of one to either lung or gastro-intestinal tract of another may be accepted as the common method by which a tuberculous individual becomes a source of danger to his neighbor, other methods of transmission occur. Contact of tubercle bacilli with vascularized tissue in any part of the body may under favorable conditions result in tubercle formation but opportunity for such invasion is scant.

Infection of young children by milk containing tubercle bacilli derived from cattle is unquestionably of less importance. The maximum incidence of such infection is well defined by investigations such as those of Park and Krumweide,[1] who have found among 478 suitably studied cases of tuberculosis only 35 with bovine tubercle bacilli and these were found in great part (25 of 35 cases) in instances of alimentary infection before the age of sixteen years.

The prevalence of tuberculosis in man and in cattle is evidence of our intimate and continual contact with the tubercle bacillus obviously increased whenever those conditions of civilization which tend to crowd people together are not counteracted by regulations to promote cleanliness of individual and community. Dread of the disease may well be diminished by realization of the truth that all of those who are exposed to tuberculosis do not exhibit evidence that they have acquired it. The adult human body exhibits notable resistance to invasion by the tubercle bacillus; in spite of the appalling frequency of tuberculosis progressive disease ending in death is in relation to the number of infections infrequent. We must distinguish between tuberculous infection and obvious tuberculous disease.

With tuberculosis as with other infectious diseases the progress of the infection is dependent upon the virulence of the infecting microorganism and upon the natural or acquired resistance of the host. In what degree does the human being possess an innate ability to resist the tubercle bacillus? Does infection cause the acquisition of immunity to reinfection? Does this type of immunity persist after the primary disease has disappeared, or, on the contrary, does the presence of the tubercle bacillus in the body as in lower animals, under certain conditions, increase susceptibility to injury by the microorganism itself or by substances derived from it? To obtain an answer to any one of these questions it is necessary to enquire into the incidence of tuberculous infection in man at various periods of life, for this evidence will furnish the basis for determining how frequently tuberculosis follows exposure to infection.

Many pathological anatomists have recorded the incidence of pulmonary and other forms of tuberculosis at different ages. The studies of Naegeli[2] and of Burkhardt[3] have attracted most attention because they have been made with great care and indicate that active or healed tuberculosis is al-

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most universal among the adult inhabitants of the cities in which these investigations were made, namely, Zurich and Dresden. During the first year of life the disease is uncommon but since tuberculosis at this period progresses rapidly and with few exceptions, quickly causes death, there is little reason for believing that congenital infection is an important source of the tuberculosrs of childhood. With increasing age, as both observers have shown, the incidence of tuberculosis steadily increases. In early childhood pulmonary tuberculosis is usually progressive and characterized by caseation which follows closely the formation of tuberculous tissue; progressive enlargement and caseation of regional lymphatic nodes occur and dissemination of miliary tubercles and tuberculous meningitis frequently precedes death. In later childhood there is greater tendency to resist the progress of the disease and in children who have died from various causes between the ages of 14 and 18 years evidence of healed pulmonary tuberculosis is common, occurring according to the observations of Burkhardt in approximately one-fourth (24%) of all children.

According to Naegeli practically all adults above the age of 18 years, namely, 97 per cent., at some period of their life have suffered with tuberculosis. Burkhardt found tuberculosis in 91 per cent. of all adults. In a fourth of those who have died during the third decade of life healed tuberculous lesions are found, and the frequency of healed lesions found increases with age being nearly a half (42%) of all individuals in the fourth decade and three-fourths (78%) at seventy years. Furthermore, it is well known that the character of the tuberculous lesion changes with age. Whereas in young children before the seventh or eighth year progressive lesions with rapid caseation and dissemination by way of the lymphatics and blood stream are usually seen, in older children and in adults chronic pulmonary tuberculosis progressing slowly from the apices of the lungs and characterized by the formation of cavities and of abundant fibrous tissue, which tends to encapsulate the tuberculous tissue is the common lesion. There is in adults little tendency to cause massive tuberculosis of regional lymphatic nodes, and disseminated miliary tuberculosis is infrequent.

The use of tuberculin as a test for hypersensitiveness to products of the tubercle bacillus furnishes further evidence of the almost universal distribution of tuberculosis among civilized races. In Vienna, Hamburger and Monti [4] found that children under one year of age convalescent from diphtheria and scarlet fever in the public hospitals, failed to exhibit a cutaneous reaction with tuberculin, whereas with increasing age the number of children which gave positive reactions rapidly increased and at the age of 12 to 14 years constituted from 93 to 94 per cent. Von Pirquet [5] in Vienna, obtained similar but slightly lower figures when cases of clinical tuberculosis were included, positive reactions being 80 per cent. of all hospital patients between ages from 10 to 14 years. Von Pirquet has determined in 328 children the relation of the cutaneous tuberculin test to the occurrence of tuberculous lesions in the body after death. In all but three of 138 children who, given a positive reaction, tuberculosis was found at autopsy, whereas no reaction had been obtained in 29 instances in which tuberculosis was found. The absence of reaction was referred to the cachetic condition at the time the test was applied. These figures representing the frequency of the tuberculin reaction obtained by Von Pirquet agree closely with those of Amenta [6] in Palermo, Italy (83 per cent. of positive reactions between the ages of 8 and 12 years), and of Calmette, Grysz and Letulle [7] (81 per cent. between the ages of 5 and 15 years). It is noteworthy that these figures correspond very closely with those representing the incidence of tuberculosis determined by Burkhardt, for tuberculosis was found in 86 per cent. of children between the ages of 5 and 10 years.

Lower figures have been obtained in this country and represent perhaps a lower incidence of tuberculosis. Among 159 institutional children between the ages of 6 and 14 years in Albany, N. Y., Shaw and Laird [8] found 45 per cent. of positive cutaneous reactions. In the St. Louis Children's Hospital Veeder and Johnston [9] tested 1321 children admitted to the hospital for all conditions. Their results were as follows:

Age.	Number of children tested.	Per cent. positive including cases of clinical tuberculosis.	Per cent. positive excluding cases of clinical tuberculosis.
0- 1	224	11	1.5
1- 2	137	24	5.5
2- 4	188	30	19
4- 6	206	33	23
6- 8	182	40	29
8-10	157	44	30
10-12	115	40	34
12-14	54	48	38

These figures suggest the possibility that tuberculosis in children is less common in St. Louis than in Vienna, where the same method produced positive reactions in 80 per cent. of children over ten years of age (Von Pirquet). Nevertheless since Monti and Hamburger have shown that the number of positive reactions is much greater with the local intracutaneous than with Von Pirquet's method of scarification, no positive conclusion is possible.

In view of the discrepancies referable to diversity of method it is difficult to obtain figures for adults comparable with those representing the frequency of the reaction in children. With the cutaneous method of Von Pirquet, Hamman and Wolman [10] in Baltimore found that 57 per cent. of adults presenting no evidence of tuberculosis gave positive reactions. This figure is comparable with

those of Von Pirquet in Vienna and of Veeder and Johnston in St. Louis, obtained by the same procedure. The percutaneous method of Moro has furnished discordant results. Wetzell[11] obtained 70 per cent. of positive reactions in non-tuberculous individuals, Emmerich[12] 32 per cent., Heinemann[13] 21 per cent., and Welb[14] 22 per cent. It is noteworthy that all of the figures are far short of those representing the incidence of tuberculosis at autopsy.

The foregoing statistics demonstrate the widespread distribution of tuberculous infection which in a large proportion of instances produces no recognizable symptom and is, indeed, a trivial malady. Tuberculosis causing clinical symptoms represents only a small proportion of instances of tuberculous infection in adults. In infancy on the contrary, progressive tuberculosis so constantly follows infection with the tubercle bacillus that a positive tuberculin reaction is evidence of the presence of grave tuberculosis. In consequence of this relation the frequency of fatal tuberculosis in infancy varies directly with intimacy of exposure to tuberculous infection. Dörner[15] found that 6 per cent. of the children of a tuberculous mother died with tuberculosis; when the father suffered with the disease the percentage of mortality from tuberculosis was only 8 per cent., and when both parents died with the disease, 10.8 per cent. But when neither parent suffered with the disease the mortality was only 2.8 per cent. Ichert[16] found that the mortality of children not removed from tuberculous surroundings was 60 per cent., whereas the mortality of children removed from tuberculous families and kept in peasant families in the country was only a fraction of one per cent.

Further proof of the efficacy of removing the new-born from the source of infection is furnished by the Bang method of controlling tuberculosis in cattle. A remarkable experiment was performed under the observation of Harlow Brooks[17] upon Holstein-Fresian cattle at Wood Crest Farm in New York. In the herd of which 425 were examined the tuberculous animals recognized by repeated tuberculin tests far outnumbered the non-tuberculous. Animals which reacted to the test were removed to a separate farm. With few exceptions tuberculous cows were bred to tuberculous bulls, the selection being made for purposes of type and in so far as breeding was concerned infection was not taken into account. At birth the calves were entirely removed from their mothers and with the exception of the first feeding derived from the mother all milk subsequently received was pasteurized. Over 200 calves had been born to the tuberculous herd and not one had become tuberculous. The object of the experiment has been to produce Holstein cattle free from tuberculous taint but possessed of the valuable characters of this breed of stock.

The infant acquires the disease when freely exposed to infection. Among adults on the contrary tuberculosis manifests so little the characters of a contagious disease that its infectious character was a matter of dispute until the experimental inoculations of Villeman furnished undisputable (though not undisputed) proof of its infectious nature. It is indeed difficult if not impossible to demonstrate by statistics that adults obviously exposed to infection suffer with tuberculosis more frequently than those who are not in contact with tuberculous individuals. Among 323 house physicians who served a term of six months at the Brompton Hospital for Consumption, C. T. Williams[18] found by investigation of their subsequent history only 12 instances of tuberculosis, yet the possibility of contact infection cannot be excluded, for among three porters employed in this hospital to handle soiled linen and destroy sputum two died with tuberculosis. Among 174 healthy physicians who had spent an average of three years in sanatorium work three and a half years later only three, according to Saugmann,[19] had suffered with tuberculosis, and no one of these had died. In the Collective Investigation Report of the British Medical Association numerous instances are cited in which one phthisical man or woman remarrying has presumably transmitted tuberculosis to several wives or husbands, but Pearson has been unable to demonstrate by carefully completed statistics that the consorts of tuberculous individuals are more prone to tuberculosis than others.

It is well known that the mortality from tuberculosis has decreased in recent years in nearly all civilized countries. In the United States, Great Britain and Prussia and other countries there has been a decrease of at least 50 per cent. within the last half century, although there has been no corresponding decrease in the death rate from other causes. Newsholme[20] has shown that this decrease began before the discovery of the tubercle bacillus and the introduction of sanatoria for the isolation and treatment of the disease. He has found a close correlation between the figures representing total paupérism on the one hand and on the other hand those representing decreasing phthisis rates of England and Scotland and the increasing phthisis rate of Ireland. Segregation of the indigent in almshouses has had an important part in limiting spread of the disease. Behla[21] has found that this decrease has occurred in the tuberculosis of adults whereas tuberculosis in children below 15 years of age has undergone no noteworthy diminution. His figures are as follows:

MORTALITY FROM TUBERCULOSIS FOR 10,000 LIVING AT EACH AGE.

	1876	1912
0 to 1 year.....	22.24	18.40
1 to 5 years.....	11.72	8.22
5 to 10 years.....	4.17	4.32
10 to 15 years.....	5.71	5.21
15 to 30 years.....	26.91	17.48
30 to 60 years.....	48.62	19.49
Over 60 years.....	77.62	19.81

Since the incidence of tuberculosis in children

closely corresponds with exposure to infection these figures of Behla suggest that the diminished mortality from tuberculosis is not referable to restricted distribution of the tubercle bacillus, but to improved conditions of living. Fischberg points out that paradoxical as it may be, the encouraging decline in the death rate from tuberculosis has been accompanied by no diminution in the number of persons infected with the tubercle bacillus, for tuberculous infection is well nigh universal.

Tuberculosis is not evenly distributed among all races. The disease was prevalent in ancient Greece and Rome, existed as a veritable scourge in the middle ages, and is now widely disseminated among the civilized nations of Europe. Among primitive races of Africa, Australia and Asia and among the American Indians tuberculosis appears to have been unknown until it was introduced by contact with more civilized white races. Maurice Fischberg,[22] who has exhaustively reviewed the subject, says: "Whenever the savage or barbarian comes in contact with the European he is bound to suffer in many ways and tuberculous infection is one of the most pernicious effects which civilization brings to primitive man." There is evidence that tuberculosis in races previously exposed to the disease has an unusually rapid course and presents lesions which suggest that there is little resistance to it. I cite this evidence in the attempt to explain by contrast the peculiar clinical and anatomical characters of phthisis and other forms of tuberculosis occurring among civilized races. By the application of the tuberculin test of Von Pirquet to great numbers of natives in certain French colonies scattered in Africa, Asia, America and Oceania, Calmette[23] found that the disease is uncommon among the native blacks in countries uninvaded by Europeans such as Senegal (for adults 15.2 per cent. of positive reactions), or Madagascar (7.1 per cent.), but development of tuberculosis occurs in direct relation to the immigration of whites and commercial interchange with Europeans (e. g. in Algeria 52.8 per cent., in Reunion 81 per cent.). At Bassam on the Ivory Coast Sorrel[24] found that 22.9 per cent. of the inhabitants reacted to tuberculin, whereas at Bornake, 350 kilometers inland, only 2 per cent. of the blacks reacted. Similar observations have been made by Ziemann[25] in German South Africa. Among adult Bantu natives the number of positive reactions did not exceed 4.4 per cent., and in all instances in which Bantu children reacted to tuberculin the parents had served in the homes of Europeans. Among eighty natives of the adjacent highlands only one positive tuberculin reaction was obtained. and this individual had served as a soldier on the coast. Similar illustrations may be obtained from the numerous observations lately made in Persia, Australia, Philippine Islands and elsewhere.

These data demonstrate that civilized and many semi-civilized races of Europe and Asia are permeated with tuberculosis, whereas primitive peoples who have not come into contact with these more civilized races may be almost wholly free from the disease. The habitat of the white races is the home of the germ which has only recently been carried to aboriginal races.

It is well established that those races which have heretofore escaped tuberculous infection are especially susceptible when they are exposed by importation of the disease. Rapidly progressive pulmonary tuberculosis similar to that which occurs in children is common among races first infected with tuberculosis, and rapidly extending caseous tuberculosis of lymphatic nodes is prevalent. The ravages of tuberculosis in recent years among the American Indians following the introduction of the disease have been described by many writers. Westenhoffer[26] describes the fatal character of tuberculosis among the Indians and half-breeds of Chile. In one-third of cases observed post mortem the disease was of acute pneumonic type and even in the more chronic cases there was little tendency to the formation of connective tissue and of large cavities. Among seventy autopsies performed upon natives of German New Guinea, Hoffmann[27] found no trace of healed tuberculosis.

In European Turkey, Deycke[28] studied the incidence of tuberculosis among Asiatics who had come from countries in which tuberculosis is absent, and found that acute miliary tuberculosis of lymphatic nodes, bones, joints and viscera is common and chronic phthisis very rare. Gilman,[29] Brewer[30] and Musgrave and Simon[31] have shown that similar acute types of tuberculosis prevail among the natives of the Philippines, pulmonary tuberculosis being less common.

In a comprehensive review of the incidence of tuberculosis among different races Fischberg cites the Jewish race to illustrate a condition opposite to that prevailing among aboriginal races. Marked resistance to tuberculous infection has followed intimate exposure to the disease through many generations. For many centuries they have lived in cities and have not engaged in agricultural pursuits. Fischberg says: "While we have no evidence that tuberculosis was frequent among them in their ancient home in Palestine 2000 years ago, nor even whether they knew the disease at all at that time, we know that their mortality rates in the medieval Ghettos were very high. . . . In the Ghetto of Vienna about one-third of the deaths from 1648 to 1869 were caused by tuberculosis. . . . Following this continued exposure to tuberculous infection the mortality from tuberculosis is at present less than that of other races, fulminating types of tuberculous puenmonia are very uncommon and the disease usually pursues a chronic course lasting from three to five or even ten or twenty years.

The tubercle bacillus may rightly be regarded as a microorganism which compared, for example, with the pyogenic microorganisms has little virulence, for it multiplies slowly in the body and produces slowly those changes which result in

the necrosis of tissues. The relatively scant virulence of the tubercle bacillus associated under certain conditions with ability to persist in the body, is well illustrated by the experiment of Bartel and Stern,[32] who showed that if human tubercle bacilli are fed to rabbits no lesions of the intestinal mucosa nor of the regional lymphatic nodes occur, but tubercle bacilli were demonstrated by animal inoculations in the mesenteric lymph nodes in one instance 104 days after feeding. Tubercle bacilli have been repeatedly demonstrated in apparently normal lymph nodes of children. The microorganism may act as a symbiotic invader. Its capacity to produce grave disease is dependent upon its ability to resist destruction in the body and this protection is doubtless dependent in part at least upon the presence of a wax-like constituent which resists solution by the lytic substances of the blood serum and the phagocytic cells of the body. The reaction which occurs in response to the tubercle bacillus often results in the formation of giant cells which are in many respects similar to those which accumulate about any insoluble foreign body introduced into the tissues. The tubercle is composed in great part of so-called epithelioid cells which are capable of ingesting tubercle bacilli, and changes which the bacillus undergoes in staining reaction, and its fragmentation into particles indicates that it undergoes destruction within these cells. Although polynuclear leucocytes are scant in the tubercle they are not wholly passive during the disease, for when tubercle bacilli are injected into an animal polynuclear leucocytes accumulate in considerable number about the free bacilli, later giving place to the epithelioid cells. Furthermore, when caseation occurs in the tubercle, polynuclear leucocytes penetrate into the caseous material and ingest tubercle bacilli which occur free in the necrotic material. In the dog which is relatively insusceptible to tuberculosis polynuclear leucocytes are particularly numerous in tuberculous tissue. Injection of tuberculin into a tuberculous animal causes the wandering of polynuclear leucocytes into the tuberculous tissue. With these observations in view I [33] have attempted several years ago to increase the resistance which an animal opposes to the progress of the disease by bringing into contact with the tuberculous lesion an increased number of exuded cells, among which polynuclear leucocytes were numerous. Tuberculous tissue produced by inoculation of large doses of tubercle bacilli into the pleural cavities of dogs in many instances melted away under the influence of washed cells obtained from sterile purulent exudates. Control animals inoculated with tubercle bacilli in equal dosage developed fatal infection. Manwaring [34] has found that the cells obtained from acute inflammatory exudates injected into the subdural space of dogs produce recovery from otherwise fatal tuberculous meningitis. In these experiments the natural resistance of the animal has been increased by aiding processes normally used to combat the invading microorganism.

Susceptibility of different tissues to tuberculous infection varies very greatly. The muscles and large blood vessels are resistant even to very severe infections. The relative infrequency of laryngeal tuberculosis when the mucosa is exposed to tubercle bacilli discharged with the sputum from the lung is noteworthy. The frequency with which different organs are affected by tuberculosis is obviously dependent upon exposure to infection as well as to special susceptibility of the tissue.

The localization of tuberculosis in the apices of the lungs, more frequently on the right side than on the left, may be regarded as an index to the susceptibility of this part of the lung to invasion by the tubercle bacillus. In childhood, when there is less resistance to invasion by the microorganism, varying vulnerability of different parts of the lung is less evident. Kuss [35] found primary pulmonary tuberculosis equally common in the right and left lungs of children; it occurred both in the upper and in the lower lobes, but rarely in the apices. Ghon [36] found primary foci somewhat more frequent upon the right side than upon the left, and more often in the upper than in the lower lobes, but the figures which he obtained approximate the proportional volume of the two lungs and their individual lobes. In adults, on the contrary, the distribution of the lesion in those dead with tuberculosis demonstrate the peculiar disposition of the right above the left and the apices above other parts of the lungs.

The usual localization of tuberculosis recognizable by its symptoms in the apices of the lungs and particularly in the right apex is dependent. I believe, not upon the peculiar liability of this part of the lung to deposition of the tubercle bacilli, but is dependent upon the inability of this part of the lung to resist the extension of a tuberculous process. Active tuberculosis usually affects the apices but healed tuberculosis is common in other parts of the lungs.

Many attempts have been made to define the conditions which determine the greater vulnerability of the apices. It is not material to the present discussion to determine if this is dependent upon insufficient aeration and retarded flow of blood or lymph caused by unusual narrowness of the ring formed by the first ribs, to abnormal shortness of the first costal cartilage, to early ossification of these cartilages or to other cause. Of more interest in the present connection is the claim that a local disposition, that is, a *locus minoris resistentiae,* may be inherited. This view was first maintained by Turban,[37] who found in 80 per cent. of patients among 55 families evidence that tuberculosis in the same family originates in corresponding situations in the lungs. Baldwin [38] has made similar observations. Kuthy [39] found that 71 per cent. of parents and children, or brothers and sisters affected with tuberculosis had lesions of similar type with similar

localization. There is little evidence in favor of the view that hereditary transmission of tuberculosis has an important part in its dissemination, but recent investigation, notably the statistical studies of Pearson, for example, leaves open the possibility that a disposition to the disease, that is, a tuberculous diathesis, may be transmitted from parent to child.

I shall attempt no comprehensive discussion of immunity in tuberculosis. I wish to present those experimental observations which are applicable to the interpretation of human lesions. No discussion of immunity in tuberculosis can omit the fundamental experiment of Koch, who demonstrated in tuberculous animals the development of immunity to reinfection. If a healthy guinea pig is inoculated below the skin with tuberculosis a hard nodule is formed after from ten to fourteen days; the overlying skin soon breaks and the ulcer persists until death. The adjacent lymphatic nodes become tuberculous. If, however, an animal previously infected with tuberculosis is reinoculated subcutaneously the site of inoculation within one or two days becomes hard and assumes a dark color, forming an area of considerable size over which the skin quickly undergoes necrosis. The ulcer usually heals promptly and there is no involvement of the regional lymphatic nodes. This modified reaction is best observed in animals which have been infected with tuberculosis during from four to six weeks. Some subsequent observers found increased susceptibility rather than immunity to reinoculation, for occasionally death followed within forty-eight hours the introduction of tubercle bacilli into an animal already tuberculous. It is now recognized as the result of studies of Boil [40] and others that death occurs when the amount of tubercle bacilli is large. This observation is in harmony with the fatal result which follows the introduction of dead tubercle bacilli or of tuberculin in considerable quantity into a tuberculous animal.

Innumerable attempts have been made to produce immunity in animals by the inoculation with tubercle bacilli of virulence insufficient to cause the death of the animal. Though previous attempts had been made to produce immunity in small animals the first notably successful experiments were performed by Dr. Trudeau [41] in 1892 and 1893. Rabbits were inoculated with cultures of avian tubercle bacilli which in some instances caused death. In animals which recovered infection with mammalian tubercle was immediately followed by an active inflammatory reaction from which recovery occurred after a number of weeks. The same culture of mammalian bacilli injected into unvaccinated rabbits caused progressive caseous lesions with extensive destruction of tissue and often fatal generalized tuberculosis. It is noteworthy that these experiments demonstrated the untrustworthy character of the immunity conferred upon the vaccinated animals, for in some of these animals there was relapse, the lesion subsequently progressing slowly. By injection of relatively avirulent human tubercle bacilli immunity has been produced to virulent strains of human or even of bovine type in apes, cattle, sheep, goats, rabbits and in the very susceptible guinea pig as well.

The vaccination of cattle against tuberculosis in view of its practical importance as a prophylactic measure has been exhaustively studied. Following the early studies of McFadyean,[42] Pearson [43] and Neufeld [44] upon the protection of cattle from tuberculosis by vaccination with living tubercle bacilli v. Behring developed a method of immunization which has been used upon such a large scale that its value is now well defined. Young cattle, preferably twelve weeks old, are injected intravenously with a human culture of determined virulence. Animals so treated after about three months are immune to infection with virulent tubercle bacilli of the bovine type. The widespread use of this method has served to demonstrate very clearly the limitations of the immunity which results, and by analogy to suggest the relative inefficiency of the immunity in man following transient lesions. It is now evident that this form of vaccination cannot be used to limit the spread of tuberculosis among cattle for the following reasons: (1) The average duration of efficient immunity does not exceed one year. (2) Following the intravenous introduction of human tubercle bacilli, tubercles are found in the internal organs and in the udder, and human tubercle bacilli may appear in the milk. (3) Whereas vaccinated animals are protected from the injurious effects of artificial inoculation with bacilli of the bovine type, tuberculosis is frequently acquired when vaccinated animals are brought into contact with naturally infected animals (so-called stall-infection).

Numerous experiments such as those of Koch [45] and his coworkers on cattle, of Trudeau [46] on guinea pigs, and of Kraus and Volk [47] studying cutaneous tuberculosis in apes, have shown that the degree of protection increases with the virulence of the tubercle bacillus employed but increased virulence subjects the animals to the danger of fatal tuberculosis. Friedmann's much exploited cure represented an attempt to incite immunity with a tubercle bacillus derived from the turtle and possessing no virulence for man. Furthermore, methods which artificially diminish the virulence of the microorganism diminish its capacity to protect from subsequent infection. It is well known that tubercles may be produced by injection of dead tubercle bacilli into animals but, though hypersusceptibility to tuberculin is produced, there is no noteworthy immunity to living tubercle bacilli. The goal of a vast amount of unsuccessful experiments has been the production of a harmless agent capable of producing immunity and a great variety of methods of destroying the microorganism have been employed, always with the hope that the subtle chemical constitution

which excites the immunizing reaction might remain unaltered.

The foregoing observations have shown the approximate truth of Löwenstein's [48] aphorism: Only the tuberculous organism is immune to tuberculosis. During this period of immunity a considerable number of immune bodies have been demonstrated in the blood serum both of animals artificially infected and in man or lower animals spontaneously infected with the disease. The presence of weak agglutinims have long been recognized. The so-called opsonic index furnishes no indication of the power of the serum to further phagocytosis by polynuclear leucocytes, but by determining the dilution required to reduce phagocytosis in the presence of serum to the level at which it occurs in an indifferent medium like salt solution. Meakins [49] has shown that the opsonic content of the serum of rabbits slowly and steadily rises to a strength five hundred times the normal. In this connection it is noteworthy that Manwaring [50] has demonstrated by exceedingly ingenious methods that opsonic substances have a part in the phagocytosis performed by endothelial cells of the liver, and the studies of Evans, Bowman and Winternitz [51] have shown that similar cells have an important part in the formation of the tubercle.

Kraus and Höfer [52] maintain that the tubercle bacillus undergoes extracellular solution in the peritoneal cavity or subcutaneous tissue of a tuberculous guinea pig within fifteen or twenty minutes, with an activity far in excess of that observed in normal animals. This lysis of tubercle bacilli is, they think, similar to that which affects the spirillum of cholera in the so-called Pfeiffer's reaction exhibited by animals immunized to this microorganism.

I shall not review the considerable literature concerning the reaction of complement-fixation in tuberculosis, but in order to bring further evidence of the occurrence of antibodies in animals immunized to tuberculosis shall cite recent experiments of Besredka.[53] In guinea pigs and rabbits infected with human tubercle bacilli the reaction of complement fixation appeared within from four to twenty days after infection, and was almost constantly present during the course of the disease, often disappearing before death. With the more virulent infections produced in these animals by the bovine bacillus the reaction failed to appear. The reaction varies with the resistance of the animal.

Studying the sheep immunized to tuberculosis Roemer and Joseph [54] found, by the methods which they employed, no one of the antibodies which have been mentioned constantly demonstrable in the serum, but emphasize the constant association of immunity and hypersusceptibility to tuberculin.

Hypersusceptibility to the action of tuberculin may be considered one of the phenomena exhibited by the animal which has become tuberculous and in consequence relatively immune to tuberculosis. The systematic experimental studies of Roemer and Joseph [55] made upon guinea pigs by use of intracutaneous reaction produced by various quantities of tuberculin have shown that the rapidity of development and intensity of the tuberculin reaction is dependent upon the severity of infection. Animals inoculated with bovine tubercle bacilli develop susceptibility more quickly and become more sensitive to small quantities of tuberculin than those which have received the less virulent human bacillus; those which have received large quantities of tubercle bacilli are more intensely sensitized than those which have been inoculated with smaller quantities. In animals with localized tuberculous processes and partial healing there is scant sensitization. Observations made upon cattle which were subjected before death to a quantitative intracutaneous tuberculin test showed a similar though less accurately definable relation between the lesion and susceptibility to tuberculin. Animals with healed calcified lesions were sensitive only to a comparatively large dose of tuberculin (0.05 cm.) whereas those with active tuberculosis usually reacted to much smaller quantities.

It is well recognized that tuberculosis of the lung produced by experimental introduction of the tubercle bacillus into the blood or into the respiratory passages does not reproduce the lesion usually found in the lungs of human beings. Many experiments have shown that tuberculosis pursues a modified course in animals whose resistance has been increased by preceding infection and the modified lesion of the lung often presents close resemblance to human phthisis.

The tendency of tuberculosis to find lodgment in the lungs varies in different animals. In guinea pigs the lymphatic nodes, the spleen and the liver become the sites of massive tuberculous lesions whereas the lungs only contain miliary tubercles and do not exhibit the caseation and cavity formation which accompany pulmonary tuberculosis of man. Orth [56] found that if guinea pigs are first inoculated with tubercle bacilli of little virulence and then reinoculated with virulent microorganisms lesions resembling human phthisis characterized by massive caseation and cavity formation occur in the lungs. Preceding infection, he thinks, has increased the local disposition of the lung to tuberculosis; localization in the lung is referable to this disposition and not to general immunity though general immunity may explain the more chronic course of the disease. Rabbits were found more prone to pulmonary tuberculosis but double infection first with human tubercle bacilli and later after an interval of from three to six months with bovine tubercle bacilli greatly increased the incidence of pulmonary tuberculosis with cavity formation, whether the second infection was by way of the subcutaneous tissue, peritoneal cavity or vein. Pulmonary tuberculosis with cavity formation has been produced by von Behring [57] and by Neufeld [58] in goats injected with large doses of virulent tubercle bacilli after relative immunization

by preceding infection. Levy and his coworkers [59] think that there is greater opportunity for cavity formation because the disease pursues a more chronic course in animals which have been immunized.

In a series of very suggestive experiments Bachmeister [60] produced local tuberculosis of the apices of the lung in rabbits. The respiratory movements of the upper part of the thorax were restrained by a wire frame in order to reproduce the immobility and compression to which some (Freund, Hart and others) have attributed the predisposition of the apices. If these animals had undergone a preceding mild infection with tuberculosis and were again inoculated Bachmeister succeeded in producing a lesion like that of human phthisis developing in the peribronchial and perivascular tissue of the apex forming cavities and progressing toward the basal part of the lung.

By numerous experiments on guinea pigs Roemer [61] has shown that tuberculosis of the lungs with cavity formation resembling human phthisis occurs constantly when a massive new infection is produced in an animal which is already infected and is immune to a smaller dose of bacilli. The same massive dose of tubercle bacilli injected into a normal animal causes disseminated miliary tuberculosis with no cavity formation in the lungs. It is not necessary to introduce a new strain of tubercle bacilli, for phthisis may be reproduced in a tuberculous guinea pig by injecting an emulsion prepared from lymph nodes removed by operation from the same animal. If the genesis of phthisis in man corresponds to that in the experimental animal it represents, Roemer thinks, the reaction of an animal long infected with tuberculosis to a massive reinfection. Whether this new infection comes from without or is caused by tubercle bacilli set free from some focus derived from the primary infection is a question to which the experiments suggest no answer. Nevertheless the experiments of Roemer demonstrate that massive infection from without is not essential to the production of cavernous pulmonary tuberculosis.

Roemer found that it was occasionally possible to produce tuberculosis of the lungs with cavities by a single infection with tubercle bacilli under conditions which permitted the gradual immunization of the animal. After inoculation of a guinea pig intraperitoneally with an exceedingly minute quantity (.00001 mgr.) of tubercle bacilli attenuated by drying (Bovovaccin) the animal lived fourteen months and cavernous pulmonary tuberculosis was found when it was killed.

The experiments of Nichols [62] on rabbits vaccinated by inoculation with human tubercle bacilli furnish significant evidence concerning the activity of the inflammatory reaction which follows reinfection with virulent tubercle bacilli; in these experiments immunity is indicated by the tendency to recovery and the limitations of this immunity are well shown by the occasional occurrence of death with advanced caseous pneumonia. Immunized animals when inoculated intravenously with virulent bovine tubercle bacilli exhibit a far more prompt and active reaction than normal animals inoculated for control. The lungs of the immunized animals become voluminous and injected and contain such numerous cellular tubercules that they exhibit the appearance of pneumonia consolidation. In the controls on the contrary tubercles are small and discrete. In the immunized animals the process reaches a maximum and subsides, there is no caseation, tubercle bacilli disappear and accumulated cells actually undergo resolution and disappear. In the control animals tubercles increase in size and undergo caseation and finally cause death. In a few instances immunization does not induce the favorable course which has been described. The animals are very ill following inoculation with virulent microorganisms and death occurred with caseous pneumonia exceeding in extent the lesions of the controls. The unusually active reaction in the immunized and coincidently sensitized animal is followed by caseation, resolution is no longer possible and the immunized animal succumbs to the intensity of its own reaction.

In a study of the lesions produced by bovine tubercle bacilli in calves previously immunized by tubercle bacilli of human type Theobald Smith [63] to whom we owe so much of our present knowledge of infection has described the peculiar histological characters of the pulmonary lesions of immunized animals and has pointed out their similarity to the changes which occur with human phthisis. In normal calves which have received bovine bacilli injected into a vein, the parenchyma of the lungs are permeated with immense numbers of tubercles which have their origin in the capillaries of the alveolar walls. In immunized animals on the contrary heightened resistance to intravenous inoculation is indicated by the localization of the lesion not in the alveolar walls but in the walls of relatively few of the bronchioles tributary to lobules situated below the pleural surface. It seems probable that a few surviving bacilli are carried from the capillaries to the peribronchial lymph channels where after a period of latency they stimulate the formation of tuberculous tissue which pushes its way into the lumen of the bronchiole. It is noteworthy that small round cells of lymphoid type predominate in the tuberculous tissue of the immunized animal whereas the epithelioid and giant cells which are abundant in non-immune animals are scant. Acquired immunity has in great part prevented the formation of tubercles arising from the bloodvessels but does not inhibit their development in lympatic tissue. After the newly formed mass has pushed its way into the bronchiole, the lobule supplied by it undergoes collapse and the alveoli are ultimately occupied by an accumulation of cells. Caseation occurs, the cheesy mass, undergoing softening, is discharged and a small cavity is formed. Theobald Smith compares the lesion which he has observed with the earliest recognizable changes in human pulmonary tuberculosis found

by Abrikosoff[64] in seven incipient lesions. This observer finds that the disease begins as a tuberculous peribronchial lymphangitis; newly formed tuberculous tissue grows into the bronchus and undergoes caseation. The aspiration of caseous masses produce pneumonic foci and softening brings about the formation of cavities. It is significant for an understanding of phthisiogenesis that, contrary to the view of Abrikosoff, the bronchial lesion is not necessarily the result of airborne infection, for in the immunized calves of Theobald Smith an almost identical lesion has been produced by bacilli brought to the lung by the blood stream.

These experiments demonstrate that the pulmonary tuberculosis of human adults who have almost invariably been infected with tuberculosis in early life can be readily reproduced in those animals which have been partially immunized by preceding infection. It is probable that tuberculous pneumonia with galloping consumption may be the result of infection of individuals who have abnormally low resistance because they have escaped infection. Observations upon the tuberculosis of primitive races give support to this view.

In a discussion of the effect of preceding infection upon the lesion accompanying reinfection sensitization to tuberculin should be considered. In the preliminary experiments which resulted in Koch's discovery of tuberculin he found that a large dose of tubercle bacilli injected into an animal already the subject of tuberculosis in some instances killed within from six to forty-eight hours. In these animals there was acute inflammation not only at the site of inoculation but surrounding each tuberculous focus throughout the body as well. The first observations of Koch upon the therapeutic effects of tuberculin, as it is well known, were made upon cases of tuberculosis of the skin. Injection of tuberculin at a distance from the cutaneous lesion produced acute inflammation of the tuberculous tissue and when the dose was large there was considerable necrosis of the diseased tissue and tendency to heal followed ulceration; with repeated injection larger doses of tuberculin were required to produce this local reaction. It is probable that the disastrous results which followed the use of large doses of tuberculin were caused by similar changes in the vicinity of tuberculous lesions of internal organs. A lesion situated near a free surface such as the lumen of a blood vessel or a serous cavity apparently tends to undergo necrosis and to slough into the cavity. This tendency may explain the appearance of tubercle bacilli in the circulating blood of tuberculous animals observed by Rabinowitsch[65] and by Bacmeister[66] after injection with tuberculin. Hence there is reason to assume that sensitization to tuberculin with its associated increase in susceptibility to necrosis in the presence of the tubercle bacillus or its products has a part in the increased tendency to cavity formation in the lungs of animals previously infected with the disease. We are presented with the paradoxical truth that preceding infection with the tubercle bacillus may increase both general resistance to the tubercle bacillus and local susceptibility to its products.

It is furthermore probable that the incidence and character of tuberculosis in organs other than the lung are modified by preceding infection. The occurrence of chronic tuberculosis localized in the kidney, epididymis, adrenal or other organ may be dependent upon this factor. Weber and Titze[67] found that chronic lesions of brain, meninges, eye, or genital organs are especially common in calves which have been vaccinated with nonvirulent tubercle bacilli and then infected with bovine bacilli. Calmette has made similar observations.

The limitation of the immunity produced by infection with tubercle bacilli is well shown by the persistence of tubercle bacilli during months in tissue which may exhibit no tuberculous lesion. Bartel[68] found that tubercle bacilli fed to rabbits are diminished in virulence after they have passed the intestinal mucosa and are still further diminished in virulence after they have reached the lymphatic nodes where they may remain latent during months; the nodes exhibit no specific tuberculous lesions but there are hyperplasia of lymphoid follicles and proliferation of cells within the sinuses of the nodes. The animal becomes sensitive to tuberculin. One of several experiments of Römer and Joseph[69] may be cited. They inoculated a guinea pig with a minute quantity of attentuated tubercle bacilli; the animal became sensitive to tuberculin and three months later tubercle bacilli were demonstrated by inoculation of the omentum into another animal although this tissue exhibited no evidence of tuberculosis.

The ability of the tubercle bacillus to persist latent in lymphatic nodes has long been recognized. Loomis,[70] as early as 1891, first directed attention to the occurrence of tubercle bacilli virulent for small animals in lymphatic nodes which exhibited no tuberculous lesions. Observations of Harbit,[71] Weichselbaum and Bartel,[72] Weber and Baginsky,[73] MacFadyen and McConky[74] and others have shown that the submaxillary, cervical, bronchial or mesenteric lymph nodes and the tonsils of children exhibiting no gross or microscopic evidence of tuberculosis may contain tubercle bacilli capable of producing fatal tuberculosis when the tissue is inoculated into guinea pigs. The persistence of living virulent tubercle bacilli in lesions which have apparently healed completely has been demonstrated by many observers among whom are Rabinowitsch,[75] Lubarsch,[76] Wegelin,[77] and others. Geipel[78] found masses of tubercle bacilli in the chalky caseous matter from five of seven calcified lesions at the apices of the lungs and in one additional instance found that an old focus had infected its vicinity with fresh tubercles.

The immunity of a tuberculous animal to rein-

fection is shown by the healing of the lesion produced by a second injection with tubercle bacilli. At the site of the second inoculation a new tuberculous lesion occasionally develops after the scar has remained unchanged for a period of two or three months; there is accompanying enlargement of the regional lymphatic nodes. This exacerbation of the apparently healed lesion described by Roemer [79] and by Hamburger [80] furnishes evidence that tubercle bacilli have persisted at the site of reinfection. Hamburger has found that the regional lymphatic nodes are in some instances the site of exacerbation and undergo swelling although the scar of reinoculation exhibits no change. Why exacerbation never occurs in some animals but occurs in another is not evident. Similar phenomena are not infrequently seen in man and may explain the lighting up of latent or even apparently healed tuberculous lesions. In view of the relationship which hypersensitiveness to tuberculin bears to immuinty the observations of v. Pirquet,[81] followed by those of Grüner [82] and others, upon the disappearance of the tuberculin reaction during measles are suggestive, for in this disease an existing tuberculous process shows an evident tendency to progress. W. Fisher has described fourteen instances in which under the influence, as he believes, of the cachexia of carcinoma apparently inactive cicatrized or calcified foci in the lungs or bronchial lymph nodes of elderly people have become active and have produced fresh tuberculosis. There is little accurate knowledge concerning the factors which determine the fate of a tuberculous lesion.

I shall present a short summary of the foregoing discussion and the conclusions which, I believe, may be drawn from it. In accordance with formerly accepted views phthisis was thought to be the result of primary infection of the lungs produced by tubercle bacilli which had been drawn into the alveoli with the inspired air. V. Behring has maintained that tuberculosis of adults begins in childhood, in his words: it is the "end of the song sung at the cradle of him who becomes consumptive." This is a conviction consoling to those who have presumably escaped the disease. It has been widely used as an argument against the phthisophobia engendered by the false doctrine that exposure to infection is necessarily followed by the disease. While it contains a large element of truth it cannot be accepted literally. Orth has described instances in which with acute tuberculous lesions there are calcified lymphatic nodes indicative of old healed tuberculosis. In one case with extensive fresh tuberculous pneumonia there was a calcified lymphatic node at the root of the right lung; that a reinfection had occurred from without was indicated by the cultivation of a bacillus of bovine type from the lymph node whereas a tubercle bacillus of human type was obtained from the pneumonia lesion. Nevertheless, Orth maintains that in the majority of those who have died with phthisis there is no focus suggestive of a lesion dating back into childhood and there is, he points out, no caseation of lymphatic nodes such as occurs in childhood and even if there are old lesions of lymphatic nodes the persisting chalky caseation or complete calcification does not suggest the possibility of massive reinfection from an old lesion. Nevertheless, observations concerning the frequency of tuberculosis at autopsy indicate that three-fourths of children before the age of 14 years have tuberculous lesions, and studies of the incidence of the tuberculin reaction indicate that ninety per cent. have been infected with the tubercle bacillus before this age.

Experiments upon animals demonstrate that there is immunity to reinfection so long as a tuberculous lesion exists in the body. When the lesion has healed completely resistance to reinfection tends to disappear. The evidence which has been cited shows that active tuberculosis is accompanied by immunization which is partially effective in preventing reinfection; this immunity opposes resistance to secondary autoinfection and modifies the progress of the primary lesion. It is probable that this immunity persists in great part unimpaired with so-called latent tuberculosis which is characterized by the complete encapsulation of a tuberculous focus by fibrous tissue and is present in the lungs or lymphatic nodes of from one fourth to one third of all adults. In what degree immunity disappears when healing is complete is as yet not accurately determined.

The evidence which has been reviewed indicates that children of civilized countries, on the one hand, and adults of those primitive races which have not been exposed to tuberculosis, on the other hand, exhibit similar reactions to invasion by the tubercle bacillus; the disease affecting the lungs pursues a rapid course, affects impartially all parts of the lungs, quickly implicates the regional lymphatic nodes and is often disseminated throughout the internal organs. Tuberculosis of adults of civilized races pursues a more chronic course, affects especially the apices of the lungs, and when progressive on the one hand results in the formation of cavities and on the other stimulates the formation of fibrous tissue which in its turn tends to limit the progress of the disease; involvement of lymphatic nodes is an inconspicuous feature of the disease and dissemination throughout the body is much less common than in childhood.

Numerous experiments have shown that the disease of childhood and of primitive man is similar to that which is produced by the inoculation of tubercle bacilli into normal animals. Experimental tuberculosis in lower animals does not reproduce human phthisis, but if animals are first immunized by tuberculous infection, reinfection of the lungs produces a lesion which more closely resembles the human disease. Susceptibility of the lung to tuberculous invasion becomes especially evident because the resistance of other organs is increased. Anatomical and physiological peculiarities of the lung determine its special disposition to the dis-

ease. The resistance to the tubercle bacillus which is conferred by tuberculous infection not only prevents infection with new microorganisms from without but retards the progress of those bacteria which are themselves responsible for this increased resistance. The progress of the lesion is retarded and dissemination of tuberculosis throughout the body is prevented. Nevertheless, immunity is only partial and reinfection with virulent tubercle bacilli or with tubercle bacilli in great number is still possible.

Coincident with the immunity to reinfection associated with tuberculosis there is hypersensitiveness to tuberculin, a product of the tubercle bacillus. There is abundant evidence in favor of the view that in spite of general immunization consequent upon a primary infection the tissues of the body acquire increased susceptibility to necrosis caused by immediate contact with the tubercle bacillus. In the classic experiment of Koch necrosis occurred within forty-eight hours at the site of reinoculation. A corresponding change within the lung, causing disintegration of infected tissue would result in the formation of a cavity. Liberation of tubercle bacilli permits their transportation by the respiratory movements to other parts of the lungs; a vicious circle is formed.

In accordance with the prevailing view supported by Baldwin,[84] Krause,[85] Austrian[86] and others, the tuberculin reaction is an expression of hypersusceptibility to the protein of the tubercle bacillus. It is analogous to the hypersusceptibility produced by horse serum and other foreign proteins but co-existing immunity associated with the appearance of agglutinin, opsonins, lytic substances and antibody with other activity retards the multiplication of the tubercle bacillus and tends to limit the progress of the tuberculous lesion. Several writers have offered the interesting suggestion that the symptoms of tuberculosis are referable to this hypersensitiveness to tuberculo-protein. It is not necessary to assume that the tuberculous focus throws out toxins in order to explain the ordinary symptoms of tuberculosis, namely, weakness, anorexia, tachycardia, emaciation and fever. Indeed, it is more rational in the light of our present knowledge to ascribe them to the absorption of products of the tubercle bacillus by the sensitized organism. "If an extract of the entire contents of several tubes of cultures of tubercle bacilli," Krause says, "will not make a normal animal the least bit ill, why should the products of comparatively few bacilli, as many as would be enclosed in a tubercle the size of a walnut, bring about so severe an intoxication of an animal?" The sensitive condition of the tuberculous individual gives an explanation.

Observations of human cases and experiment on lower animals demonstrate that immunity conferred by tuberculous infection is imperfect and transient, for it is overcome by virulent or massive infection and diminishes, if it does not disappear, after complete recovery from the primary infection. Although a large proportion of children are infected before puberty the evidence available does not demonstrate that tuberculous infection occurs only in childhood. Recognition of the partial immunity conferred by tuberculosis may well combat extravagant phthisophobia engendered by irrational propaganda undertaken with the laudable purpose of controlling the disease. The prevalence of tuberculosis among marble workers, tobacco handlers and others subjected to continuous inhalation of dust, the diminution of tuberculosis in the English army in the middle of the last century following regulations increasing the space assigned to soldiers in barracks, suggest but do not demonstrate that infection may occur in adult life. The factors which diminish resistance to infection are not understood.

The wide difference in susceptibility which exists between the adult population of civilized and of primitive people offers some interesting problems concerning the prophylaxis of the disease. Is the resistance of races long exposed to tuberculosis the result of almost universal infection with the disease? Some have questioned the desirability of complete elimination of infection. Would it render the community susceptible to the most acute types of infection whenever the disease is reintroduced? There is no reason to believe that immunity to tuberculosis is transmitted from parent to offspring and there is no convincing evidence to support the view that heredity is an important factor in the transmission of the disease itself, but it is by no means impossible that disposition or natural resistance may be inherited. Almost universal dissemination of the disease may serve to eliminate those who are predisposed to it and perhaps by continued selection produce a race with considerable resistance. Nevertheless, it is noteworthy that there is little resistance in early childhood. These hypothetical possibilities furnish no argument against the obvious immediate advantage of diminishing the incidence of tuberculosis. Available evidence proves that we may trust natural processes to immunize by mild infection, a large proportion of all human beings. It is evident that efforts directed to the limitation of infection in early childhood offer the greatest prospect of success. Poverty and its associated evils appear to provide those conditions which most frequently transform mere infection into a disease.

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